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| 10/820,091 | 04/07/2004 | Yulu Wang | 94350-00005 | 7131 |

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| EXAMINER | |
|---|---|
| SELLMAN, CACHET I | |

| ART UNIT | PAPER NUMBER |
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| 1762 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/820,091 | WANG ET AL. | |
| | Examiner | Art Unit | |
| | Cachet I. Sellman | 1762 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 May 2007*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I claims 1-28 in the reply filed on 5/22/2007 is acknowledged.

### *Claim Objections*

The objection to claim 17 is withdrawn due to applicant's amendment to the claim.

### *Claim Rejections - 35 USC § 112*

The 112 second paragraph rejection of claim 4 and 6 is withdrawn due to applicant's amendment to the claims.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-2, 4-11, 20-22 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Subramanian et al. (US 5833891).

Subramanian et al. ('891) teach a supercritical fluid process for the coating ultra-fine drug (col. 5, line 6) particle (0.6 micrometer) with polymer (col. 25, claim 21, 22), comprising: preparing a solution of a polymer in an organic solvent, such as acetone (col. 22, line 51), suspending a quantity of ultrafine particles in said solution; and combing a supercritical fluid as antisolvent, such as CO2, (col. 5, line 30) with said suspension to cause at least a portion of said quantity of suspended ultrafine particles to precipitate from said solution as polymer-coated ultrafine particles (abstract and col. 18, line 65 paragraph of "particle coating "). Subramanian et al. ('891) further teach a variety of core particles can be used in the process (col.7, line 9-15) such as glass or sugar beads or medicament in any discrete solid dosage forms can be coated.

Subramanian et al. teaches the use of hollow micro spheres which can have the particle size of less than 50 (μm) which overlaps the range as described by the applicant for nanoparticles. Subramanian et al teaches that the solution can be less than 4.0 mg/ml (i.e. 2 mg/ml) as shown in Table 2.

This process has many applications in all areas, for example, pharmaceutical application, pesticide application, polymer application and conductive ink application (col. 22, line 39-44 and col. 23, line 1-8) as required by **claim 2**.

As for **claim 4**:

Subramanian et al. ('891) teach the polymer coating would be from about 1-30% by weight of the final coated product (col.7, line 20-21).

The polymer can be a polyactic acid-glycolic acid polymer (Examples 1-4) as required by **claim 5**.

As stated above the particles include at least one drug and the coating functions to control the rélease of that drug as required by **claim 6**.

As for **claims 7, 8 and 22**:

Subramanian et al. ('891) further teach (col. 5, line 5-12) the method involving contacting the drug-polymer dispersion solution with antisolvent at its supercritical fluid condition and cause the antisolvent to deplete the dispersant and precipitate the substance as fine particles. Condition enhances the mass transfer rate between the antisolvent and the dispersant so that particle nucleation and precipitation occur rapidly. Then, (Col. 10, line 13-19) the precipitated polymer-coated drug particles are purged with supercritical fluid until the organic solvent is completely depleted from the system (col. 7, line 43-46). The antisolvent is bone dry CO2 (99.8% purity) (col.13, line 10).

As for claims 10,11,26 and 27:

Subramanian et al. ('891) teach using an apparatus (page 14, Figure 2) for this coating process involving passing the fluid drug-polymer dispersion solution through first passageway into the high-pressure vessel containing the antisolvent (col.5, line 45-59). Simultaneously, an "energizing gas" steam is passed along the second passageway

into said vessel. A high-energy sonic wave device is used for break up agglomerates of polymer coated drug particles (col. 5, 60-67).

As for claims 18, 20:

Subramanian et al. ('891) further teach the "energizing gas" is the same as the selected antisolvent, and in most cases carbon dioxide is used both as the antisolvent and "energizing gas" which may be selected from the group consisting of nitrogen, carbon dioxide, propane, trifluromethane and mixtures thereof (col. 6, line 31-43). As disclosed in the above the same supercritical fluid been used as the antisolvent.

5. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Subramanian et al. as applied to claim1 above in further view of Lee (US 6596206).

Subramanian et al. ('891) teach that which is disclosed in the above.

Subramanian et al. ('891) teach use supercritical carbon dioxide as the antisolvent and fail to teach using supercritical ammonia or a combination of supercritical fluids as the antisolvent in the SAS process of encapsulation of drug ultrafine particles.

Lee ('206) teaches a SAS process to generate ultra fine particles (about 5 nm to 2.5 um in diameter) of a pharmaceutical agent (col. 7 line 9-47), wherein the solvent is an aqueous or an organic solvent, such as acetone (col.8, line 65), and the antisolvent is a supercritical fluid (col. 16, claim1). Lee (' 209) further teaches (col.5, line 2-7) when the antisolvent is admixed with the solution of drug in solvent; the solubility of the drug can be reduced to the point at which it precipitates out of solution. The antisolvent is

supercritical fluid (col. 10, line 1-15) selected from the group consisting of carbon dioxide, ammonia and combinations thereof (col.16, line 43-54).

Both Subramanian et al ('891) and Lee ('206) utilize supercritical fluid as anti-solvent to prepare fine particles of polymer and drug. Supercritical fluids such as ammonia, carbon dioxide and combination thereof are commonly utilized in the art as evidenced by Lee ('206). One having ordinary skill in the art would recognize that choice of one or the other supercritical fluid is depended on organic solvent, which is used to dissolve polymer, solubility in the supercritical fluid. The antisolvent must be at least partially miscible with the organic solvent such the antisolvent is capable of penetrating into polymer solution to cause the desired precipitation of the polymer. Since both Lee ('206) and Subramanian et al ('891) utilize acetone as the organic solvent, therefore, it would have been obvious to one having ordinary skill in the art to utilize supercritical ammonia or a combination of supercritical fluids as taught by Lee ('206) in the method of Subramanian et al ('891) to produce polymer coated drug particles as the supercritical ammonia is easily available and might cost less too.

6. Claims 1, 5-8, 10, 11, 14-18 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al. (US 6620351).

Gupta et al ('351) teach a method (col. 6, line 35-55) of using a supercritical fluid as the antisolvent to encapsulate ultra fine particles with polymer (col. 14, line 64-66) to form composite nanoparticles, comprising preparing a solution of polymer, poly (lactide-co-glycolide) in dicholormethane; suspending magnetite nanoparticles (particle size is about 10 nanometer) in said solution (col. 15, line 4-6). The apparatus used in the

teaching of Gupta et al. ('351) consisting a particle-polymer dispersion solution delivery system, an antisolvent supply system and a particle production high-pressure vessel (sheet1 of 25, Fig. 1). The particle-polymer dispersion solution is pumped to the high-pressure vessel through a nozzle at a predetermined flow rate (page 9, line 28-41) and the antisolvent, CO2, is delivered to the bottom of this high-pressure vessel through another pump. The high-pressure vessel is filled with the antisolvent up to the desired operating pressure (page 9, line 53-60) and combining the particle-polymer dispersion with the antisolvent cause at least a portion of suspended ultrafine particles to precipitate from said solution as polymer-coated ultrafine particles. Gupta et al. ('351) further teach this apparatus is equipped with an energy source to cause the vibration (col.9, line 41-44) on a surface within the particle production vessel, and a vibration force can be applied to the particle-polymer dispersion solution to break up agglomerates of ultrafine particles formed.

Gupta et al. teaches using a polymer concentration of 5 mg/ml in an example which is not that of the claimed range of less than 4.0, however, the ranges are close and it would have been obvious to one having ordinary skill in the art to modify the concentration through routine experimentation in order to insure proper coating of the particles especially since Gupta et al. does not limit or show criticality in using the particular concentration.

As for claims 7 and 8:

Gupta et al. ('351) teach (col.10, line 24-26) the flow rate of CO2 is maintained high enough so that all the solvents in the dispersion are removed to obtain dry particles.

As for claims 14-17:

Gupta et al. ('351) teach the size (col. 6, line 17-20) of the ultrafine particle depends on the process parameters, such as pressure and temperature of the antisolvent and concentration and flow rate of the polymer solution.
Gupta et al. ('351) teach encapsulating drug particle with poly (lactide-co-glycolide), PLGA (Tg= 40-55C), with antisolvent, CO2, at pressure of 96.5 bar (9.68 MPa) and at temperature of 35 C, which is below the glass transition temperature (col.14, line 60-64) of the polymer therein. Examiner notice this is the similar pressure, 8.96 MPa, which was chosen in the instance application on page 17, [0185] for minimizing agglomeration of coated particles.

7. Claims 1, 2, 11, 18 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perrutt (US 2003/0031784).

Perrut ('784) teaches a method of encapsulating very fine particles (page 1, [0012]) with a coating agent, i.e. a polymer, ethylcellulose (page 4, [0054]) by a method employing a supercritical pressure. Perrut ('784) teaches dissolving ethylcellulose in ethyl acetate and mixing amoxicilline particles into the polymer solution, then combining a supercritical fluid, CO2 with the solution to cause at least a portion of suspended particles to precipitate from solution as polymer-coated particles. Perrut ('784) teaches the 4.5% of ethylcellulose in ethyl acetate in the process (page 4, [0054]), the density of

ethyl acetate is about 0.897 g/ml at room temperature. Therefore, 4.5% is about 5.08 mg/ml of polymer in solvent. Perrut ('784) teaches the concentration of the coating agent in the solvent will preferably sufficiently low to avoid a precipitation giving rise to the formation of agglomerates. The ranges are close and it would have been obvious to one having ordinary skill in the art to modify the concentration through routine experimentation in order to insure proper coating of the particles especially since Gupta et al. does not limit or show criticality in using the particular concentration.

As for claims 2 and 18:

The fine particle is amoxicillin, and the supercritical fluid is carbon dioxide (page 4, [0054]).

As for claim 22

Perrut ('784) teaches (page 3, [0034]) the supercritical fluid percolating within the polymer solution and cause the organic solvent loses a large part of its solvent power. Perrut ('784) further teaches (page 3, [0037]) due to the percolation of the supercritical fluid in the solution, the polymer passes into oversaturation and consequently, precipitates on the particles to coat them.

8. Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perrut as applied to claims 1 above in view of Lee.

Perrut ('784) teaches that which is disclosed in the above. Perrut ('784) teaches encapsulation fine particles of amoxilline with ethylcellulose in a SAS process. Perrut (''784) is silent about formulate the drug particles with diluent or fill such as lactose, dextrose, cellulose and combinations thereof.

Lee ('206) teaches that which is disclosed in the above. Lee ('206) further teach the pharmaceutical agents that are known candidates for administration using dry powder inhalation therapy include, peptidyl drugs and analgesics (Col. 7, line 9-11). Pharmaceutical formulation typically includes components other than the active agent (Col.7, line 51-53) such as a carrier, dextrose, sucrose and fructose (col. 7, line 55-60). Other additives commonly included in a particulate pharmaceuticals included diluents, stabilizers and lubricants (col. 8, line 1-4). For controlled release particles, a biodegradable polymer, such as a polyethylene glycol (page 8, line 29), may be incorporated into the solid particles prepared according to the disclosure above. The weight ratio of the diluents can vary from about 0.1 to 1 about 100,000 to 1 depending upon the application (col.8, line 12-14).

Lee ('491) teaches a SAS process for producing a formulated drug particle not specifically for coating a fine solid drug particle. However, it will be readily apparent to persons skilled in the art, the SAS process for particle formation and for particle coating are similar, except that in coating applications the host particles are suspended in the polymer solution before being delivered into SC CO2. It would have been obvious to one having ordinary skill in the art to use the formulated drug particles consisting of filler and diluents of the teaching by Lee ('491) in the method of Subramanian et al. ('891) to produce polymer encapsulated drug particles in a similar SAS mass transfer process.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cachet I. Sellman whose telephone number is 571-272-0691. The examiner can normally be reached on Monday through Friday, 7:00 - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Timothy Meeks can be reached on 571-272-1423. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cachet I Sellman
Examiner
Art Unit 1762

cis

***/William Phillip Fletcher III/***
Primary Examiner